"10 DAYS EXTENDED COURSE OF CLOMIPHENE CITRATE IN WOMEN WITH OVULATORY DISORDERS"

THESIS
FOR

DOCTOR OF MEDICINE
(OBSTETRICS & GYNAECOLOGY)

BUNDELKHAND UNIVERSITY,
JHANSI (U.P.)

2005 **GOURI ROY**

Dedicated

to

My Parents

CERTIFICATE

This is to certify that the work entitled "10 days extended course of Clomiphene citrate in females with ovulatory disorders" which is being submitted as a thesis for M.D.(Gynaecology & Obstetrics) Examination 2005 of Bundelkhand University, Jhansi, has been carried out by Dr. Gouri Roy in the Department of Gynaecology and Obstetrics, M.L.B. Medical College, Jhansi.

The method described was undertaken by the candidate himself and the observations recorded have been periodically checked. She has put in the necessary stay in the Department as per University regulations, and has fulfilled the conditions required for the submission of thesis according to University regulations.

Dated: 13/10/04

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CONTENTS

Introduction

INTRODUCTION

Human sub-fertility and infertility have been source of personal misery. The desire to procreate is universal. Childlessness may be tragedy to the married women and can be a cause of marital upset as well as a personal unhappiness and ill health.

The having of children cements a marriage. Childlessness were once and still are in some communities, regarded as a. disgrace, as a mark of Divine displeasure, as grounds for divorce and even for compulsory suicide on the part of female only.

Term infertility is defined as involuntary childlessness after one year of unprotected conception (WHO). It excludes the period during which contraception is used.

Infertility may be primary or secondary. Primary infertility – If conception has never occurred. Secondary infertility - If patient fails to conceive after having produced a child or had an undoubted miscarriage.

Incidence of infertility in general population is 10-15%. Pathological infertility may be due to male factor alone i. e. 8-22% or female factors alone i.e. 25-37%. Both may contribute for 21-38% of cases. In 8-14% of cases no cause is detected (FIGO Manual, 1990). Infertility due to female factors alone may be due to tubal factors i.e. responsible for 36-44% of cases, due to ovulatory' factors i.e. responsible for 26-44% of cases and endometrial factors that are responsible for 1-100/0 of cases (FIGO Manual, 1990).

As ovulation is an obvious prerequisite to conception, ovulation must be documented as part of the basic assessment of the infertile

couple. A women with regular menstruation at approximately 4.5 wk interval with monilial symptoms such as premenstrual breast swelling/tenderness and dysmenorrhoea almost invariably have ovulatory cycles. Ovulation may be documented by menstrual history, daily charting of basal body temperature, endometrial biopsy to know the hormonal status, Cervical mucus study, transvaginal ultrasonography and hormonal study of plasma progesterone and leutinizing hormone.

Ovulatory disorder may be oligoovulation i.e. infrequent ovulation or may be anovulation i.e. complete absence of ovulation. Ovulatory disorders may be due to menstrual defect at any level of hypothalamic pituitary ovarian axis or due to other endocrinological causes as thyroid disease, adrenal or hypoadrenergic oligoovulation.

According to level of defect in hypothalamus, pituitary or ovary ovulation is induced. If hypothalamic and pituitary functions are normal, clomiphene is drug of choice.

In patient with ovulatory function infertility with hyperprolactinemia treatment with bromo-criptin is added to ovulation - induction. Addition of Dexamethasone to ovulation induction regimen for women with hyperandrogenism and ovulatory factor infertility is beneficial.

Women who fail to ovulate or to become pregnant with clomiphene citrate as well as after addition of bromocriptin or dexamethasone and in woman with hypogonadotrophic hypoestrogenic anovulation i.e. defect at pituitary level are treated with human menopausal gonadotrophins i.e. follicular stimulating honnone and leutinizing honnone, combination or follicular stimulating honnone alone or combination of clomiphene citrate with HMG.

Patients with hypothalamic failure with functional pituitary and ovaries are the best candidates for ovulation induction with gonadotrophin releasing hormone GnRH.

Other treatment modalities to ovulatory disorder as in polycystic ovarian is wedge resection of ovary. In luteal phase dysfunction clomiphene and progesterone are given.

Out of the various modalities used for ovulation induction, clomiphene citrate is the first line of treatment. It is the simplest, least expensive, safe and non invasive form of ovulation. Clomiphene citrate is a non-steroidal compound, weak synthetic estrogen but it acts clinically as an estrogen antagonist for ovulation action at typical pharmacological doses. It binds to the cytoplasmic estrogen receptors and thus acts as antiestrogenic in humans. It induces gonadotrophin (Gn) secretion by blocking feedback inhibition of the pituitary and also antagonises some of the peripheral actions of estrogen. The ovaries respond to Gn stimulation by producing ovulation.

Success rates with the use of clomiphene citrate for ovulation induction are excellent i. e. ovulation rates of 80-85% and conception rates of 40%. The discrepancy between ovulatory rates and conception rates is most likely secondary to the presence of additional, nonovulatory infertility factors. Most pregnancies occur during the first 6 months of therapy.

Clomiphene citrate is typically used for ovulation induction in following manner - the drug is supplied in 50 mg tab. The usual starting dose - is 50 mg/day from day 2 or 3 after the spontaneous menstruation or progesterone withdrawal bleeding and is continued upto 5 days.

If ovulation does not occur at the initial dosage, the dosage is increased in each subsequent cycle by 50 mg/day may be given upto 250 mg/day. In the present study Clomiphene is used for 10 days in 100 mg doses in patients not responding to standard 5 days regimen with the theme that duration of therapy may be more important to its success than the total dose of clomiphene citrate per cycle and it is cost effective too.

Aims and Objectives

AIMS AND OBJECTIVES

To provide 10 days extended course of clomiphene citrate to poor infertile couples those who don't respond to 5 days standard dose of clomiphene citrate.

Review of Literature

REVIEW OF LITERATURE

For the successful conception and ovulation whole of the genital tract must be anatomically normal and physiologically healthy. Before proceeding toward treatment of any female for infertility, cause of infertility must be detected, whether it is failure of ovulation or hostile mucus or any other defect in genital tract related to tubes or uterine cavity. Ovulation failure is most common type of treatable cause of infertility. There are various methods to determine the ovulation and response of ovulation induction.

In 1987 Michael Vermish, Ascad A. itzby, Val Davajan and Robert Israel presented monitoring techniques to predict and detect ovulation. Various methods were: Daily transvaginal ultrasonography, rapid measurement of S.leutinizing hormone, S. estradiol hormone levels, determination of urinary LH Kit with and recording of basal body temperature. The result demonstrated that 'Transvaginal Ultrasound' detected ovulation in all cycles.

Various methods, drugs, regimens are described by different authors to treat the ovulation defects. Most commonly used drug for ovulation induction is clomiphene citrate.

It was first synthesized in 1959 and was known as compound MRL/41. Unexpected and interesting biological activity in the field of reproduction

MRL/41 - Proprietary name of clomiphene citrate. physiology was encountered while evaluating an experimental compound MRL/41 as an infertility agent. In the rat, this compound has been known to have

pituitary gonadotrophic inhibiting and antifertility properties. Instead MRL/41 was found to possess a surprising potential for the induction of ovulating type cycle in amenorrhic female.

Robert B. Greenblatt, William E. Barfield, Edwin C. Jungech and Albert W. Ray in 1961 first employed this compound for ovulation induction in doses of 25-50 mg 2 or 3 times per day for period ranging from 8 days to 8 months.

They concluded their results as :

1. MRL/41, an analogue of non steroidal estrogenic, substance chlorotriansene (TGGE) appear to have a wide spectrum of biological activity. No toxic reaction of haemopoietic, renal, hepatic function have therefore been detected.

2. MRL/41 is not a progesterone like substance. This may be deduced from the fact that the thermogenic response was noticed only in the luteal phase of cycle in spite of continuous administration of the compound.

3. An anti estrogenic effect has been suggested by the occurrence of hot flushes in quite a few patients and by the fact that regressive changes took place in vaginal mucosa.

4. A salient feature of this drug is its apparent ability to modify pituitary ovarian imbalance in the human with resultant induction of ovulatory type menses. Such an action was evidenced by the secretory changes in the endometrium. The inhibition of ferning of cervical mucus and sustained corpus luteal effect as noted by prolonged thermogenic effect before the onset of menstruation.

In the same year Kistner, R.W: and Smith, O.W. used MER-25, another nonsteroidal estrogen antagonist for the ovulation induction. But this drug proved to be too toxic for use and was withdrawn from clinical trial.

In 1966, Fluker, Wang, Rowe carried out a study on 30 cases. They prescribed clomiphene citrate for 10 days and ovulation was observed in 47% of cases.

In 1974, Rust, Israel, Daniel and Mishell described individualized graduated therapeutic regime of clomiphene citrate starting from 50 mg x 5 day/cycle and increased upto 250 mg/day x 5 day. Ovulation rate was 91.4% and conception rate was 38.1%. Most of those who failed to conceive had additional infertility factors. When these multiple infertility factor are eliminated, pregnancy rate in clomiphene treated patients was 85.7%.

In 1976, James Evan & Laule Townsend described the different methods of induction of ovulation. Treatment plan utilized placebo, cyclical steroid therapy, clomiphene citrate and human pituitary gonadotropin for the induction of ovulation in carefully selected potentially fertile females. Successful ovulation was induced in 99.5% and pregnancy rate was 61.9%. The success rates for ovulation with placebo therapy was 35%, with cyclical steroid therapy was 18.4%, with clomiphene citrate was 80.7% and with gonadotropin it was 100%. Pregnancy rate was recorded 56% with clomiphene citrate and 92% with gonadotropins.

Herlihy et al in 1981 presented their experienced with 30 cases, out of which 21 ovulated after receiving 50-250 mg clomiphene citrate upto 25th day of the cycle. In the same year Lobo et al. tried clomiphene

citrate for long duration i.e. upto 8 day 100 mg/day. Ovulation rate was 62%.

Garcia-Florus and Vazquez Mendez studied in 1984 the effect of progressive increasing doses and duration of clomiphene citrate in anovulatory cases. Majority of patients (85.7%) ovulated within the first 3 cycles after receiving 100 mg of clomiphene citrate from day 5th of menstrual cycle. Remaining cases except one ovulated after receiving 150 mg clomiphene citrate/day from day 5th to increasing duration upto 25th day.

In the same year (1984) Douglus C. Daly Walter Salo Albors concluded their randomized study on use of clomiphene citrate with dexamethasone in induction of ovulation when only clomiphene was used as standard regime, out of 22 only 14 cases ovulated but when used with dexamethasone all cases had evidence of ovulation.

In Jan. 1988, Davis and Ravnikar used high doses of clomiphene citrate in combination with prednisone and oval micronized-estradiol for premature ovarian failure.

In March 1988 Ronen, Bauchiecter, Wiswedel and Hendrinhs used clomiphene citrate in combination with low dose human menopausal gonadotropin for ovulation induction for in vitro fertilization. Results concluded in successful ovulation with 27.80/0 pregnancy rate.

In Jan 1988 Kaloszar and Bartfal used human menopausal gonadotropins in pulsatile manner for ovulation induction. In Aug. 1988, Flemming Haxton & Hamilton used combined gonadotropins releasing hormone analogue and exogenous gonadotropin for ovulation induction in infertile females. In the same year Bacchi Modena, Vadlana Fiaschetti

and Chiarazza used gonadotropin and gonadotropin releasing hormonal analogue both, in pulsatile manner for induction in chronic anovulatory patients.

In Jan 1989 Bonmaventuera described the practical aspect of ovulation induction. He used pergonal at the fixed doses. The overall pregnancy rate was 59%. He also described that use of this regime in private practice appears to be safe and effective.

In April 1989 Quartero Dixon Westwood, Licks and Chapman used pure FSH in chronic low dose pulsatile through subcutaneous route and through intramuscular route in polycystic ovarian disease for ovulation induction. They concluded that chronic low dose pulsatile administration of pure FSH has no advantage over chronic low dose intramuscular administration.

Stilnovic, Jurekovik, Grljusic and Ivanbovic in April 1989 used combination of clomiphene and human gonadotropins for ovulation induction.

Authors stimulated 21 cycles in 14 females. Ovulation was proved in 20 cycles of the combined stimulation. Altogether 11 pregnancies of all induced cycle were obtained.

Schivardi, Falsathi, Omodei and Jumla in September, 1989 used pulsatile intravenous gonadotropin releasing hormone for ovulation induction. Ovulation occurred in 93.7% of treatment cycles. No over stimulation or any other serious complication was noted. In conclusion, therapy with GnRH provides an elevated probability of therapeutic success.

Letlerric & Miyazawa in 1989 used combination of gonadotropin-releasing hormone agonist and human menopausal gonadotropins for ovulation induction in a patient with premature ovarian failure. A paradoxical suppression of ovarian. response was noted despite increasing, doses of human menopausal gonadotropins.

Burger, Hompes, Korsen and Schoemaker in Jan. 1989 used LHRH in pulsatile manner in women with clomiphene citrate-resistant polycystic ovarian disease and concluded the significant positive results. In 1990 Mizunuma, Obara, Yamada and Ibuki studied the role of pulsatile LH-RH administration for ovulation induction. Zorn, Cedard and Janseens described the clinical use of LHRH analogue for ovulation induction in 1990. In 1991 Hedon, Bringer, Boolot, Audibert, Benos, Bachelard, Neveu and Nares also described the use of LHRH analog in ovulation induction with success.

Michioka, Kobayashi, Narimatsu, Yamashita & Yakabe in 1990 described the ovulation induction in polycystic ovarian syndrome. Successful induction of ovulation in patients with PCOS was observed in treatment cycles with daily subcutaneous injections or pulsatile subcutaneous administration of human .menopausal gonadotropin (hmG) and bromocriptine, or the combination of clomiphene citrate and hmG.

In May 1990, Check Nowroozi, Chase, Hazari, Shapse &Vaze used human menopausal gonadotropins to induce ovulation in women with hypergonadotropic amenorrhoea. Ovulation was achieved in 19% of cycle. The pregnancy rate was 5.2% of ovulatory cycles. Coney, Gibbons, Christiansen & Sjulin in 1990 reviewed the results of ovulation induction in patients with ovulatory dysfunction and luteal phase defect/short luteal phase. 86 patients received clomiphene citrate for minimum of 4 cycles,

13 patients conceived. Fifty patients were offered additional therapy with human menopausal gonadotropins. Seventeen completed a minimum of four cycles and 13 conceived. The number of clomiphene citrate treated patients with poor mucus quality in the face of adequate follicular development was 48%. In summary close monitoring during ovulation induction to confirm ovulation and assess mucus quality and luteal function allow detection and correction of inadequate response. Induction of ovulation can be highly successful if patients can follow thorough and complete protocols of therapy.

In Dec. 1990 Goroda, Williams, Danforth and Hodgen gave a novel regimen of gonadotropin releasing hormone (GnRH) antagonist plus pulsatile GnRH for controlled restoration of gonadotropin secretion and ovulation induction.

Homburg, West, Torresani & Jacobs (1990) had a comparative study of single-dose growth hormone therapy as an adjuvant to gonadotropin treatment for ovulation induction. Protocol is one intramuscular injection of biosynthetic human growth hormone (24 IU) administered on the first day of gonadotropin treatment for ovulation induction. It significantly augmented the ovarian response to gonadotrophic stimulations in 7 patients. Compared with a protocol involving six smaller dose had an immediate but highly significant effect in reducing the amount, duration of treatment and daily effective dose of HMG needed to induce ovulation. The difference between the effect of the one dose and six dose protocols was small. The action of growth hormone on the human ovary, probably mediated by insulin like growth factor appears effective in enhancing the response to gonadotropin therapy even when given in a single dose.

Homberg West Obsergaard & Jacobs in 1991 had studied successful uses of growth hormone and gonadotropin for ovulation induction.

Bringer, Lmoret, Hedon and Lefebvre in 1994 explained the use of growth hormone in ovulation induction. There are increasing evidence for local ovarian action of growth hormone due to presence of receptors for GH in human granulosa cells. The ability of GH to enhance estradiol (E2) production by human granulosa cells withdrawn in late follicular phase. In the same year Katz E. emphasized the use of growth hormone in enhancing the ovarian response to gonadotropins. It reduces the effective gonadotropin dosage.

Porcile, Gallardo & Venegas in 1990 presented the role of bromocriptine in normoprolactinemic anovulation nonresponsive to clomiphene citrate. With bromocriptine alone, ovulation occurred in 28.6%. In same subjects when bromocriptine was subsequently added with clomiphene citrate - 50% ovulated.

In year 1991 various methods of ovulation induction in polycystic ovarian syndrome were described. Neyro Barrenetxea, Montoya & Rodriguez in 1991, used pure FSH for ovulation induction in PCOD patient. Ovulation rate was 83% and pregnancy rate was 36%.

Mizunuma, Takagi, Yamada, Andoh, Ibuki & Igarashi studied the effect of step down administration of purified urinary follicle stimulating hormone in PCOD patient. Kupferminc, Lessing and Peyser induced the ovulation with hMG and HCG.

Krause, Moller and Goretzlehner in 1991 described the possibility of ovulation induction using Naltrexone in women with hypothalamic

amenorrhoea. In 1992, Sir Alba Riveral Devoto described the use of chronic administration of naltroxone in patient with secondary hypothalamic amenorrhoea.

Lydic & Jacobs in May, 1992 studied the comparative effect of Nafarelin versus Leuprolide in ovulation induction for in vitro fertilization. afarelin acetate administered by intranasal route and Leuprolide acetate as subcutaneous route. The use of Nafarelin acetate may decrease a patient's hMG requirement and increase the number of frozen embryos available for later transfer as compared with Leuprolide acetate.

'0' Amato, Vizziello and Faniza in 1992 observed the effect of pulsatile administration of GnRH, in patients with polycystic ovaries. The paper reports the result of 12 ovulation induction cycles using GnRH micropump without and after GnRH analogues.

In 1992, Meldrum highlighted the ovulation induction protocols for in vitro fertilization. Ovulation induction protocols for oocyte retrieval have evolved from clomiphene citrate/human menopausal gonadotropins alone and finally, a combination of human menopausal gonadotropins and an agonist of gonadotropin releasing hormone, the almost abandonment of clomiphene use is due to findings from studies that showed reduced implantation due to the anti estrogenic effect of clomiphene. The use of GnRH-a was introduced to maintain low levels of leutinizing hormone late in follicular development to prevent premature ovulation or premature senescence of the oocyte. The long GnRH-a/hMG protocol is currently used for most patients to prepare for oocyte retrieval.

Suginami, Kitagawa, Nakahashi, Yano and Matsubara in 1993 gave a novel therapy for ovulation induction i. e. clomiphene citrate and

Tamoxifen citrate combination. Rate of ovulation was 75% and pregnancy rate per ovulatory cycle was 8.6_. All the pregnancies were normal and single. None of the treatments was combined by any remarkable side effects.

In 1993, Homburg described the ovulation induction in gonadotropin resistant women. The treatment strategies offer only partial solution to specific subgroups of poor respondent. It include protocols of clomiphene/HMG, mini- dose-GnRH agonist regime and co-treatment with GH, each of which may be found to be effective in individual cases.

Polycystic ovarian syndrome is a challenge for physician. Various methods of ovulation induction are described from time to time for PCOD patients. In year 1993, Dale, Tanbo, Lunde and Abyholm described the use of low dose follicular stimulating hormone with ovulation rate of 35% and pregnancy rate of 22%. Bregieiro, Moura, Ferriani and Bailao in 1993 described the low dose of pure follicular stimulating hormone using a fixed protocol of 75 IU/day for 8-10 days from 2nd or 3rd day of cycle. HCG was given when follicular diameter reached more or equal to 18 mm, resulted in 100% ovulation.

It was concluded that fixed protocol of low dose pure FSH produces good results, especially combined with hCG, which is effective upto 48 hr after last injection of FSH. Buckler, Critchley, Cantrill, Shalet, Anderson and Robertson in 1993 evaluated the efficacy of low dose purified FSH in ovulation induction following pituitary desensitization in polycystic ovarian syndrome. They concluded that regardless of the starting dose the use of pure FSH in. patients with polycystic ovarian syndrome, where LH has been completely down regulated may be associated with multiple follicular development and poor outcome. Their

results strongly suggest that a basic minimum amount of LH is necessary for normal ovulatory development.

In the same year Turhan, Artini, Ambrogio, Droghini, Battaglia and Genazzani had a comparative study of three ovulation induction protocols in polycystic ovarian disease patients.

Patients were treated with :

1. Clomiphene citrate plus gonadotropin (hMG).
2. Pure follicular stimulating hormone plus human menopausal gonadotropin
3. Pure FSH/HMG plus gonadotropin releasing hormone analogue (GnRH-a).

Conclusion of the study show although the suppression of the hypothalamic-pituitary ovarian axis with gonadotropin releasing hormone-a in PCOD patients improved follicular synchrony and oocyte maturity. None of the ovulating induction protocols was superior to the others with respect to pregnancy rates and pregnancy outcome.

Greenblatt in 1993 described the surgical options in polycystic ovary syndrome patients who do not respond to medical ovulation induction. For women who fail to respond to clomiphene citrate therapy, and for whom gonadotropin therapy is unsuccessful or unavailable, surgical therapy should be considered. There is a very limited role, if any, for ovarian wedge resection (OWR) in the treattnent of anovulation due - to PCOS. Although effective in inducing ovulation in approximately 80% of women, with pregnancy rates approximately 60%, OWR requires major surgery and is associated with significant adhesion formation. Newer less invasive techniques are emerging for the anovulatory women those who fail to respond medical. management. These include

laparoscopic ovarian cautery and laparoscopic ovarian Laser vaporization. These surgical techniques can be combined with diagnostic laparoscopy. Knowledge of the long term effects of these techniques is still limited but results appear promising, with spontaneous ovulation being initiated in 70 to 90% of women. The patients those remain anovulatory or oligoovulatory after these procedures, must would have been rendered sensitive to clomiphene citrate. Conception rates approximate 60%. The mechanism of action remains uncertain but is likely to involve alteration of the intraovarian steroid environment and in turn, the feedback to the hypothalamic-pituitary axis. The overall result is normalization of gonadotrophine and follicular microenvironment, allowing follicular recruitment and development to proceed to ovulation. The risk of post operative adhesion formation and the role of second look laparoscopy in the prevention of this undesirable complication remains uncertain.

In 1994, Smitz, Devroey, Mannaerts, Coeling, Bennink and Vansteir Tlegnem tested recombinant FSH for ovulation induction. They concluded supraovulation for IVF was successful and safe by using recombinant FSH alone or in combination with various GnRHa dosage and protocols.

Franks and Hamilton Fairley in 1994 described the role of body weight and metabolic anomalies in ovulation induction. Obese women with polycystic ovary syndrome require higher doses of gonadotropins for induction of ovulation than their lean counterparts. They also have lower rate of ovulation and higher prevalence of miscarriage.

Dickey and Holtkamp in 1996 reviewed the development, pharmacology and clinical experience with clomiphene citrate. The study

describes clinical observation of patient characteristics (age, additional infertility, diagnosis, semen quality). Vaginal ultrasound observations of ovaries (number and size of pre-ovulatory follicles) and endometrial lining (thickness pattern) in 2841 clomiphene cycles in patients who required intrauterine insemination because of poor sperm quality or an unsatisfactory post coital test. The result shows that (i) conception in clomiphene citrate cycle is related to the number and size of pre-ovulatory follicles, endometrial thickness, patient age, pelvic adhesion type of anovulatory disorder and semen quality. (ii) Pregnancy rates per clomiphene IUI cycle are constant throughout last six cycles (iii) multiple births cannot be prevented by with holding human chorionic gonadotrophin or advising against coitus when multiple pre-ovulation follicles are present unless all follicles down to 10-12 mm diameter are counted. They also reviewed pregnancy outcome (number of gestational sacs, preclinical and clinical abortion, ectopic pregnancy and birth sex) in 1744 clomiphene pregnancies. They found that: (i)preclinical and clinical abortions are increased only slightly by clomiphene use; compared to spontaneous pregnancy; (ii) clinical abortions are decreased in patients with polycystic ovaries and luteal insufficiency who use clomiphene; (iii) conception and preclinical abortion are related to endometrial thickness prior to ovulation; (iv) ectopic pregnancies are not increased by clomiphene and (v) the ratio of male births is not altered by clomiphene except possibly in timed insemination cycles. These studies repudiate many misconceptions regarding clomiphene. They also showed that clinical outcome may be improved by preovulatory ultrasound monitoring of ovarian and endometrial response.

In 1996, Hugues, Cedrin, Avril, Bulwa, Herve and Uzam gave the sequential step up and step down dose regime, an alternative method for

ovulation, induction with follicular-stimulating hormone in polycystic ovarian syndrome. In this study, infertile, clomiphene citrate resistant polycystic ovarian syndromes patients were treated with FSH in usual manner. The dose was reduced by half when the leading follicle reached 14 mm in diameter.

Decreasing the FSH dose following step up follicular selection may be an alternative method to avoid multifollicular development.

Silverberg in 1996 suggested ovulation induction in ovulatory women as a controlled ovarian hyperstimulation as emperic therapy for the treatment of unexplained infertility. Treatment prescribed in the form of either clomiphene citrate or gonadotropins. It is often combined with intrauterine insemination and offered to patients as a less expensive and less invasive alternative to the assisted reproductive technologies. Published data suggest an improvement in pregnancy rates when compared to expected management.

Kettle and Hummel in 1996 presented their experience on ovulation induction in the estrogenized anovulatory' patients. In estrogenized women there are many different techniques to reverse the condition of chronic anovulation. With clomiphene citrate, upto 80% of patients will ovulate and approximately half will conceive. In women those who do not respond to clomiphene therapy, injectable gonadotropins are usually successful in inducing ovulation. New protocols for administrating these powerful agents have minimized the risk of ovarian hyperstimulation and multiple pregnancy when medical therapy fails to result in successful ovulatory cycles. Surgical treatments can be considered. Laparoscopic ovarian ablation or conventional ovarian wedge resection are the method of choice.

Fluker, Wang and Rowe in 1996 gave an extended 10 days course of clomiphene citrate in women with clomiphene citrate resistant ovulatory disorders. They offered 100 mg of clomiphene citrate from 3rd day to 12th day. Ovulation occurs in 65% of cycles and conception in 17% of females. Conclusion is that it is a simple, non-invasive and inexpensive alternative for a subset of women with ovulatory disorders that are refractory to standard CC treatment.

In the same year Gol, Gurso Y, Karabacak and Yildirim used clomiphene citrate for 3 days with 50 mg/day to decrease the peripheral antiestrogenic effects of clomiphene citrate. Result in study and control group (50 mg/day cc for 5 days) showed that ovulation in study group was 82.53% while in control group ovulation rate was 95%. But pregnancy rate in study group was 17.3% while in control group was 10.5%.

Peled, Rabinerson, Kaplan, Harel and HOD in 1996 July gave a interesting word - A "sweet" indication for ovulation induction. In diabetic patient, euglycemia at the time of conception is crucial for the success of the pregnancy. In consideration of the difficulty in achieving and maintaining tight glycemic control for long period. They administered clomiphene citrate, which is usually indicated in cases of absent or infrequent ovulation, to enhance the fecundibility. All conceived within one to three cycles of the drug. No effect of the drug on the diabetes was noted as based on measurements of glycosylated haemoglobin and fructosamine concentrations and the absence of changes in the patients' insulin requirements. In the light of these beginning of diabetic pregnancIes a new "sweet" indication for the use of clomiphene citrate is added.

Trott, Plouffe, Hansen, Hines, Brann and Mahesh in Sept. 1996 evaluated the effect on ovulation of a Ist day course of dexamethasone initiated concurrently with a 5-day course of clomiphene citrate in CC-resistant patients with normal dehydroepiandrosterone sulfate levels. The study results in ovulation in 11 women out of 13 and five clinical pregnancies were achieved.

Laonaprasitipom, Barbieri and Yeh in 1996 suggested the sole use of clomiphene citrate in late-onset 21-hydroxylase deficiency for ovulation induction. Late onset 21-hydroxylase deficiency (21-0HD) is a congenital enzymatic defect in the glucocorticoid and mineralocorticoid steroidogenic pathways. The manifestations including, hirsutism and infertility, usually occur with 21-0HD. The usual therapy is glucocorticoids for ovulation induction. In this study patient was treated with clomiphene citrate alone for ovulation induction and she was conceived in her 4th cycle.

Roozenburg,. Vandessel, Evers and Bots in Aug. 1997 had successful induction of ovulation in normogonadotrophic clomiphene resistant anovulatory women by combined naltrexane and clomiphene citrate treatment. 19 patients out of 22 patients ovulated and resumption of a regular menstrual cycle was achieved and in 12 out of 19 a singleton pregnancy was observed. In conclusion, ovulation can be induced successfully using naltroxane alone or naltroxane in combination with an antiestrogen in clomiphene citrate resistant anovulatory patient. Compared to goandotropin induction of ovulation. This method is safe, simple and inexpensive.

Orvieto, Homburg, Farhi, Bar-Hava and Ben-Rafael in 1997 gave a new concept of co-treatment with human growth hormone and

menotropins in ovulation induction protocols. Follicular development in the primordial and preantral stages is almost completely independent of gonadotropins or steroids and is mainly dependent on growth factors and local regulators. Since human growth hormone was found to facilitate ovarian response to gonadotropin stimulation. So treatment with human GH prior to menotropin administration may be useful to improve results for poor responders to gonaootropins.

Messinis, Milingos in 1997 discussed the current and future status of ovulation induction in polycystic ovary syndrome. Clomiphene citrate remains the first line of treatment for all anovulatory women with PCOD, since in properly selected cases, the cumulative. pregnancy rate approaches that of normal women. Human urinary gonadotropins have been used extensively for ovulation induction, but the development of low dose regimes has opened a new era in the management of anovulation related to PCOS. Other method including pulsatile gonadotropin releasing hormone and GnRH agonist, Recombination gonadotropins, GnRH antagonist, controlled leutinizing hormone secretion. Disorders of ovulation resulting in impaired fertility constitute one of the most common cause of involuntarily childlessness. Medication facilitate ovulation, have been in clinical use for last two decades. An increasing number of patients are being conceived during or shortly after therapy with these agents. It is relevant, then, to determine whether the use of ovulation induction places a pregnant women at greater risk of an abnormal outcome, such as spontaneous abortion, fetal malfonnation or intrauterine growth retardation.

The reproduction toxicity of ovulation inducing drugs are analysed from time-to-time by different authors. Before going in details of toxicity of clomiphene citrate or other ovulation inducing drug, first come to know the mechanism of action of Clomiphene citrate.

Clomiphene citrate is a non-steroidal compound, weak synthetic estrogen but it acts clinically as an estrogen antagonist for ovulation action at typical pharmacological doses. It binds to the cytoplasmic estrogen receptors and thus acts as antiestrogenic in humans. It induces gonadotropin (Gn) secretion by blocking feedback inhibition of the pituitary and also antagonizes some of the peripheral actions of estrogen. The ovaries respond to Gn stimulation by producing ovulation. Conception occurs in women suffering from anovulation infertility.

In 1986, Anthony R. Scialli, discussed the toxicity of clomiphene citrate, human menopausal gonadotropins and bromocriptine.

He described ovulation induction with clomiphene citrate may cause luteal phase defect with consequent failure of implantation or early pregnancy loss this may be due to the anti estrogenic action of this medication within the preovulatory follicle or on the endometrium. There are few adequately controlled studies on the possible adverse pregnancy effects of clomiphene citrate. It appears, however, that once pregnancy is established, the only complication reproducibly related to clomiphene citrate therapy is an increase in twinning and miscarriage. Fetal growth and development appears to be normal in these pregnancies.

Bromocriptine therapy may successfully induce ovulation in hyperprolactinemic women. Published experience does not identify a risk of adverse pregnancy outcome attributable to the medication. Although it has been said that bromocriptine should be stopped as soon as possible after a diagnosis of pregnancy is made, a number of cases in which high dose bromocriptine is continued through much of pregnancy have not identified a hazard of this medication for the fetus.

Melvin L. Taymor, Clinical Protection Department of Obs. & Gynae.,Harvard Medical School and Beth Israel Hospital, Boston, Massachusettes published a paper on use and abuses of clomiphene citrate in 1987.

The primary indication for clomiphene citrate administration is to include ovulation in the ,infertile anovulatory patients with normal estrogen.

Production often clomiphene citrate administration is the first approach used either without a complete workup or even after a work up without a demonstration of anovulation. Even when the diagnosis of anovulation is made and clomiphene citrate prescribed, a number of abuses are common. The proper approach to therapy of clomiphene citrate requires starting at a relatively low dose, continuing the same dose as long as ovulation occurs, and increasing the dose only if there is no ovulatory response.

Other abuses stem from a failure to seek and then correct the possible cause of conception failure in the face of ovulation. One should repeat an endometrial biopsy after 3 month of clomiphene citrate therapy to be sure that a luteal phase defect has not been created by clomiphene citrate. This can be corrected by the addition of progesterone vaginal suppositories. A post coital test should be repeated during therapy to be sure than an anticervical mucus effect has not taken place. Levels of dehydroepiandrosterone sulfate and prolactin should be measured to rule out adrenal and pituitary contributions to the anovulation.

One of the other widely proclaimed abuses of CC is in treatment of luteal phase deficiency. Down & Gibson reported that if the endometrium was 5 days or more out of phase there was a significant response to

clomiphene citrate. But where endometrium was less than 5 days out of phase clomiphene citrate did not help. In cases of leuteal phase defect without a short leuteal phase progesterone vaginal suppositories rather than clomiphene citrate should be the first approach to therapy.

A final abuse of clomiphene citrate is its use in the treatment of unexplained infertility. All the evidence suggests that if a woman has a normal spontaneous ovulation one cannot make it move normal by driving the pituitary harder. All one does is sometimes create a luteal phase defect or cause an adverse effect on cervical mucus, both of which have antifertility effects.

Tucker in 1996 reviewed the reproduction toxicity of ovulation induction. No doubt that pregnancy rates have been improved with the use of agents such as : clomiphene citrate, human menopausal gonadotropins (HMG) with gonadotropic-releasing hormone (GnRH) and its analogue. These drugs stimulate the development of multiple ovarian follicles and increasing the number of fertilizable oocytes.

The negative effects from superovulation can occur during follicle development, decreasing the number of healthy oocytes and embryos capable of leading to viable pregnancy. Ovulation induction can lead not only to higher incidence of spontaneous abortion, and multiple and ectopic pregnancies, but also to poor pregnancy rates, due in part to asynchrony between embryonic development and the uterine environment. Disease such as hyperstimulation syndrome resulting in the secretion of supraphysiological levels of estradiol, .can lead to severe health complication, possibly requiring hospitalization. Most drugs used for ovulation induction can lead to ovarian hyperstimulation syndrome (OHSS). Although incidence of OHSS following CC use are less

frequent, CC has been associated with hot flushes, multiple gestations, visual disturbances, cervical mucus abnormalities and luteal phase deficiency. Finally there are reports that links any or all of the ovulation inducing drugs with a higher incidence of ovarian and breast cancer, however cause effect relationship has yet to be proven.

Material and Methods

MATERIAL AND METHODS

The present study was carried out in the Department of Obstetrics and Gynaecology of Maharani Laxmi Bai, Medical College, Jhansi in one year period since Ist Sep 2003 to 31st August 2004.

Criteria for Selection of Patients

1. Complaint of infertility
2. Patients in age group 20-35 years.
3. Met the criteria for WHO Group II ovulatory disorder:
   - (i) oligomenorrhae/ amenorrhae
   - (ii) Evidence of endogenous estrogen production
   - (iii) Normal prolacting level
   - (iv) Normal FSH
4. Patients resistant to clomiphene citrate standard regimen i. e. fail to ovulate after treatment with clomiphene citrate in doses of 150 mg/day for 5 day/cycle.

All the selected patients subjected. to detailed history, general, systemic and pelvic examination.

History

Name

Address

W/o

F/L

House No.	Colony	City
Village	Post/Thana	Distt.
Age:	Wife	Husband

Occupation & Income: Wife Husband

Marital status: Married for years

Type of infertility: Primary/Secondary

Gynaecological History

-Menarche

-Menstrual cycle

- Duration of period
- Past
- Present
- Cycle Flow
- Dysmenorrhoea

-Last menstrual period

Obstetrical history

- Parity
- Abortion/MTP/D&C

Medical History

History of tuberculosis, urinary tract infection, pelvic infection, sexually transmitted disease, liver or heart disease, endocrinological disorders, drug allergy, diabetes, hypertension, smoking, alcoholism.

Past surgical history

- Appendicectomy - Any pelvic surgery

Personal History -

Family History- any significant disease

Sexual History

. Frequency of intercourse

. Dysparunia

. Contraception: Type Duration

Previous Treatment for Infertility.

- Clomiphene
- Gonadotropin
- Others
- Surgical
- Examination
- General Appearance
- Pallor
- Height & Weight
- Endocrine status .
- Hair distribution
- Breast development - Discharge
- Obesity
- Pigmentation, ACNE
- Thyroid

Gynaecological Examination

External Genitalia	------	Labia majora
	--------	Labia minora
Per speculum	---------	Vagina
		Cervix
Per vaginum		Cervix - direction
		Uterus - Size, Shape, Version,
		Mobility
		Adenexa: Tenderness
		Thickening
		Any mass

Investigations

-Hb%

-TLC -DLC -ESR

- Blood sugar: -Fasting

- Post parandial

- VDRL: -Husband:

- Wife

- Urine examination (Both partners):
    - Routine
    - Microscopy
    - Urine culture and sensitivity

. Endometrial biopsy: Premenstrual or 1 st day of period.

. Hystrosalpingography/Sonasalpingography for tubal factor

. Diagnostic laparoscopy: For tubal and peritoneal factors (if required).

. Base line ultrasound study

. Husband's semen analysis
    - Volume
    - Count
    - Motility
    - Morphology

. Testicular biopsy - If azoospermia

Endocrinological Investigations

S. FSH S. LH	2nd day of period if required
S. Estrogen S. Prolactin S. TSH, T3, T4	
S. Progesterone -	21 st day of period, if required

Transvaginal sonography

- Follicular monitoring -
- Endometrium
- Ovulation

Ultrasonography was done first on the 2nd day of cycle from the base line study to know the status of ovaries and endometrium or to detect any other pelvic pathology.

Follicular monitoring was standard from 7th or 8th day of cycle daily till the evidence of ovulation seen.

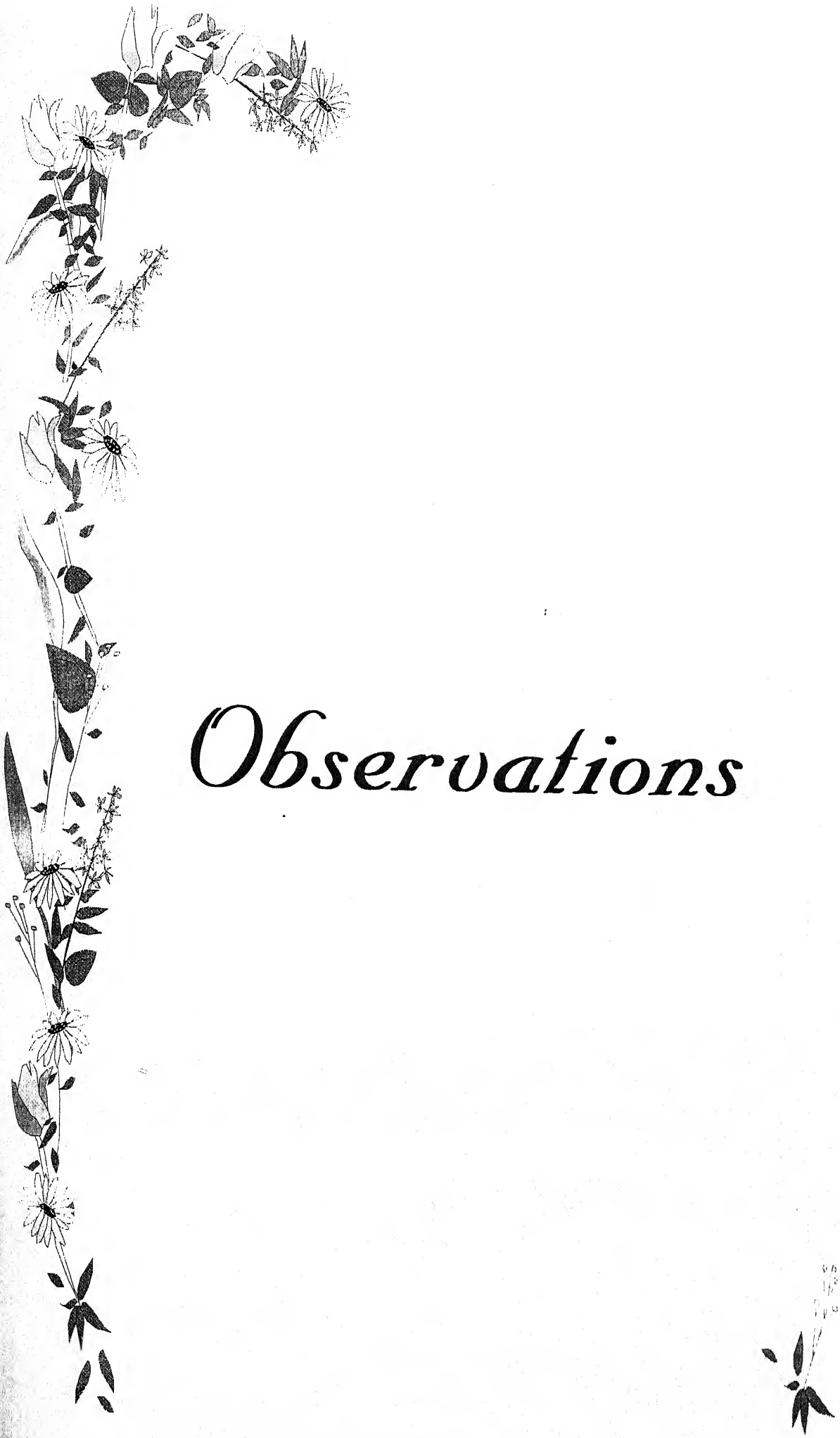
During the monitoring we determine the follicular development in both ovaries, endometrial thickness and ovulation.

Follicular Development

- Number of follicles
- Rate of growth
- Mean Diameter of follicles in two dimensions Ovulation
- The potential signs of impending ovulation are:
- Presence of a dominant follicle (usually more than 16-18 mm)
- Anechoic area double contour, around the follicles (possible ovulation with in 24 hours)
- Separation and folding of the follicle lining (ovulation within 6-10 hours)
- Thickened proliferative endometrium.

ENDOMETRIUM

Sakamoto described the characteristics sonographic image noted through the menstrual cycle in 1985. The proliferative endometrium is characterised by: (a) the presence of a well defined three line sign; (b) a hypoehogenic functional layer; (c) A minimal or absent posterior acoustic enhancement. The full endometrial thickness (full thickness of both layers of endometrium) was measured.



Observations

OBSERVATIONS

The present study was carried out on 80 infertile couples selected from those attended infertility clinic at MLB, Medical College, Jhansi between 1 st Sep. 2003 to 31st Aug. 2004. Comparative study had been conducted between the clomiphene citrate 5 days and 10 days extended courses for ovulation induction.

In our study 80 infertile couples were studied and various factors were compared.

Table 1: Distribution of cause of infertility according to Sex

Cause of infertility.	*Cases*	
	No.	*Percent*
Female factor alone	44	55
Male factor alone	8	10
Both	20	25
Unexplained infertility	8	10
Total	**80**	**100.0**

As shown in Table -1 Females were responsible for 55% of cases of infertility. Males alone were responsible for 10% of cases of infertility. In 25% of cases both were accused and in 10% of the cases, no cause was detected.

Distribution of Casuse of Infertility according to Sex

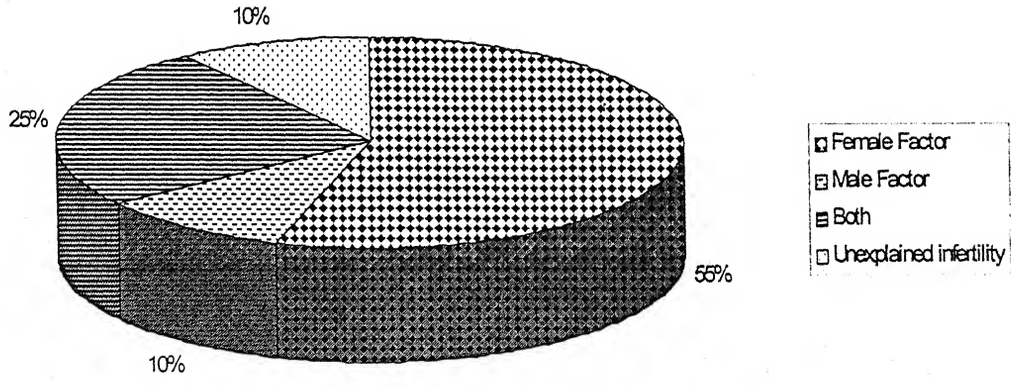


Table 2: Incidence of Primary and Secondary Infertility

Type of Infertility	*Cases*	
	Number	*Percent*
Primary infertility	62	77.50
Secondary infertility	18	22.50
Total	**80**	**100.0**

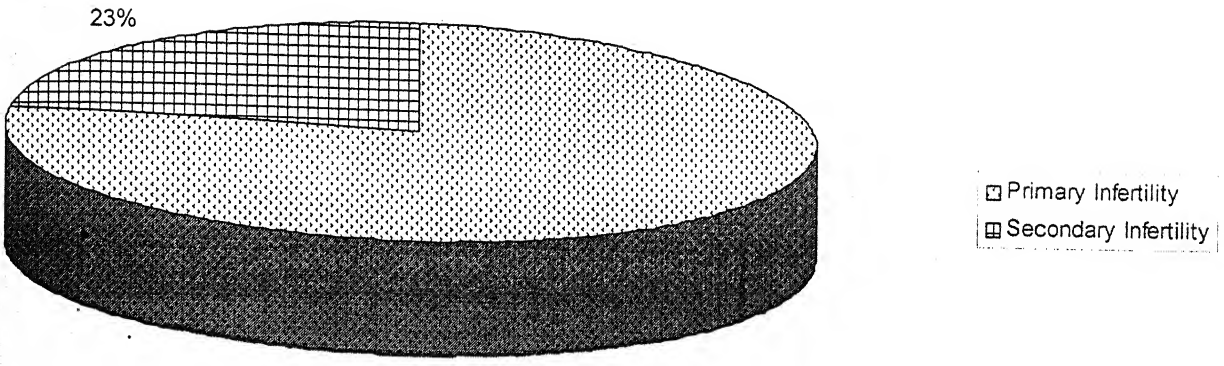
As shown in Table 2, out of 80 couples 62 (77.50%) couples were suffering from primary infertility and 18 (22.50%) couples showed secondary infertility. The difference between the both groups was significantly high.

Table 3: Distribution of cases according to age

Age in years	*Primary infertility*		*Secondary infertility*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
21-25	30	46.4	1	5.44	31	38.75
26-30	22	35.5	11	61.1	33	41.25
31-35	10	16.1	6	33.33	16	20.00
Total	**62**	**100**	**18**	**100**	**80**	**100**

Table 3 shows the incidence of infertility was observed maximum in 26-30 years of age group i. e. 41.25%. Secondary infertility was most common in the same age group (61.1%). Incidence of primary infertility was maximum in 21-25 years of age group, then decreases with age (Table 3).

Distribution of Incidence of Primary and Secondary Infertility



Distribution of Cases According to Age

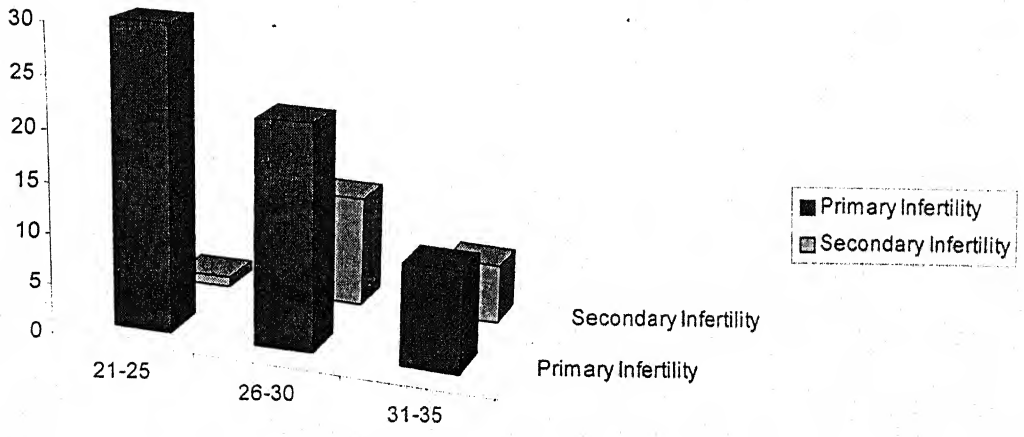


Table 4: Distribution of cases according to duration of marriage

Duration of infertility(years)	*Primary infertility*		*Secondary infertility*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
<5	29	46.78	3	16.67	32	40.0
6-10	22	35.48	8	44.44	30	37.5
11-15	7	11.29	4	22.22	11	13.75
16-20	4	6.45	3	16.7	7	8.75
Total	**62**	**100**	**18**	**100**	**80**	**100**

Table 4 shows maximum incidence of infertility was in first 5 years of marriage. Primary infertility was seen maximum in first 10 years of life rather we should say that maximum couples consult during this period. Thereafter, incidence of primary infertility declines while the incidence of secondary infertility was at peak during 5-15 years after marriage. Before and after this period incidence of secondary infertility was lower.

Distribution of Cases According to Duration of Marriage

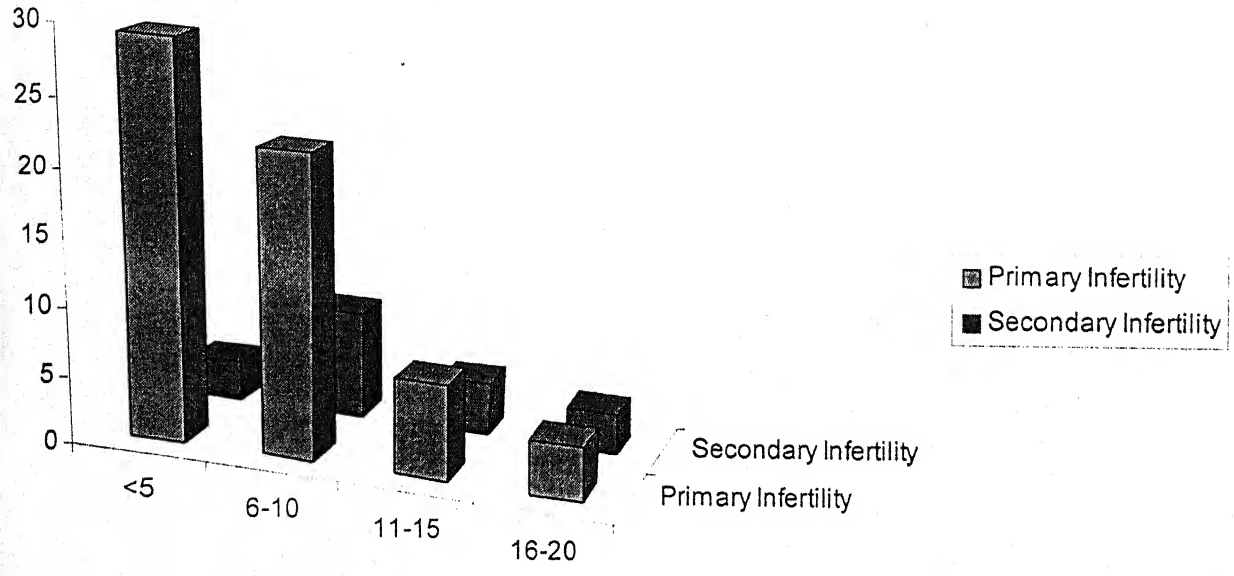


Table 5: Distribution of cases according to cause of Infertility

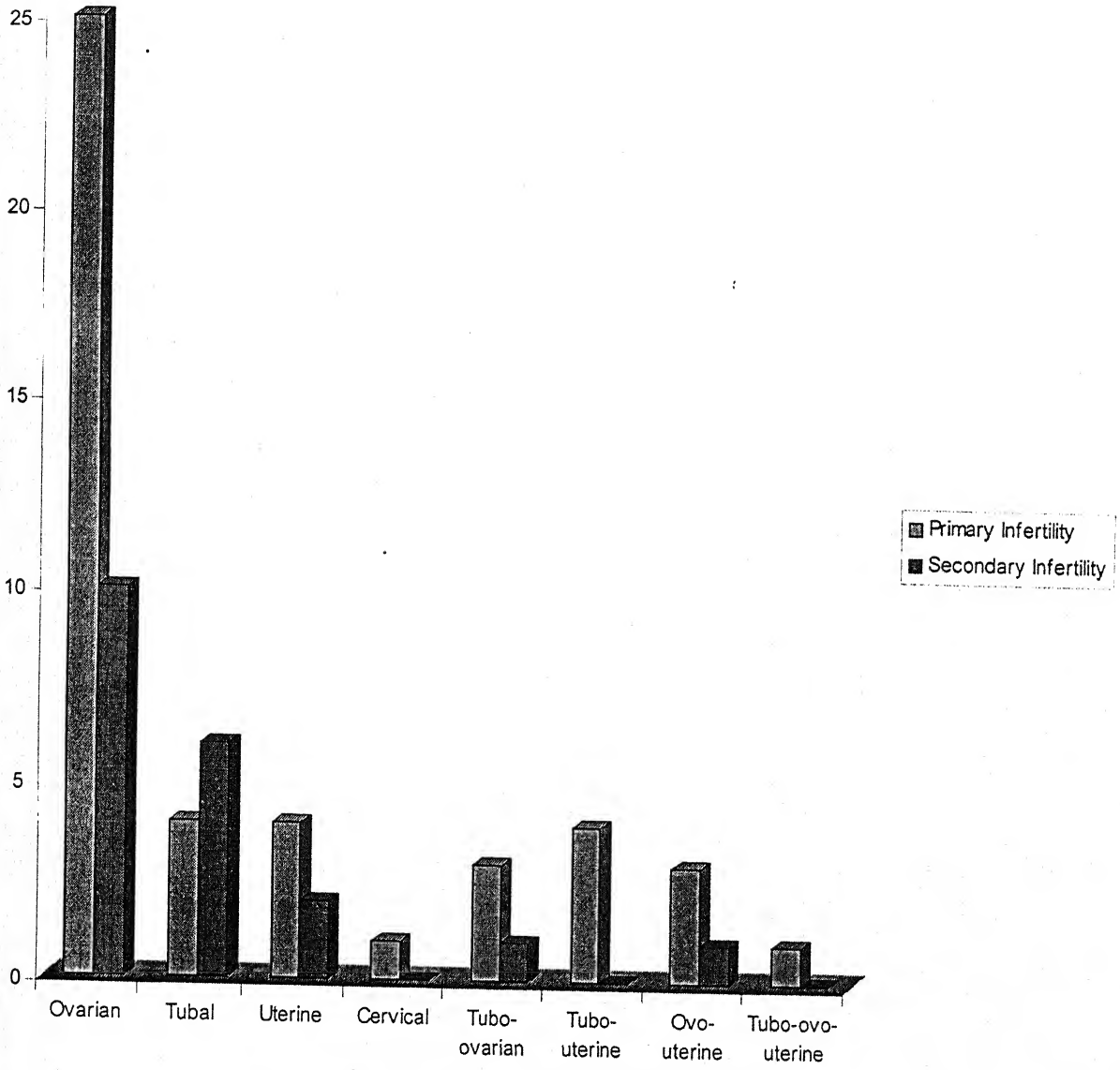
Cause	*Primary infertility*		*Secondary infertility*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Ovarian	25	55.55	10	50	35	53.85
Tubal	4	8.89	6	30	10	15.39
Uterine	4	8.89	2	10	6	9.23
Cervical	1	2.22	-	-	1	1.54
Tubo-ovarian	3	6.67	1	5	4	6.15
Tubo-uterine	4	8.89	-	-	4	6.15
Ovo-uterine	3	6.67	1	5	4	6.15
Tubo-ovo-uterine	1	2.22	-	-	1	1.54
Total	***45***	***100***	***20***	***100***	***65***	***100***

As shown in Table 1, female were responsible in 80% cases of infertility. There might be female factor alone or in combination with male. In female most common cause of infertility was ovulatory defect. It was responsible for more than 50% (n=54) of cases in both primary and secondary groups of infertility.

Tubal factors were responsible for 15.3% (n=10) of cases. Tubal factors were more important in secondary infertility i.e. responsible for 30% (n= 10) of cases while in primary infertility tubal causes were less than 10% (n=4).

Uterine causes were responsible for 10% of cases in both primary and secondary infertility groups.

Distribution of Cases According to Cause of Infertility



Cervical cause was seen in only one case of primary infertility and no case of secondary infertility due to cervical factor was detected.

As a whole, there were 35 cases in which ovulatory defect was detected, in 10 cases tubal factors were responsible, 6 cases were labelled. as uterine defect and one case was having cervical factor abnormally.

There were few cases, where more than one factor was responsible for infertility. In 4 cases tubal as well as ovarian cause was detected. In another 4 cases tubal and uterine both factors were responsible and other 4 cases ovarian and uterine both factors were accused. There was one case in which tubal ovarian and uterine - 3 factors were responsible for infertility. The same case was also suffering from male factor infertility.

Table 6: Size of follicle before ovulation

Treatment Given	*Average size of follicle*
CC x 5 days	19.8 mm
CC x 10 days	21.2 mm

Table 6 shows that average size of follice in patient treated with 5 days course of clomiphene citrate was 19.8 mm and in pt treated with 10 days course of CC was 21.2 mm.

Table 7: Showing Average day of Ovulation

Treatment Given	*Average day of ovulation*
CC (x 5 days)	14
CC x 10 days	15

Average day of ovulation in CC x 5 days was 14 days while CC x 10 days was 15 days.

Table 8: Ovulation Rate

Type of therapy cases	*Total Number of*	*Ovulation*	*Percentage*
CC x 5 days	35	20	57%
CC x 10 days	15	10	66.6%

In our study 15 cases were treated with clomiphene citrate 100 mg x 10 day after showing resistant to 5 day course up to in 150 mg/day. Out of 15, 10 cases had evidence of spontaneous ovulation in first cycle of 10 days, course of clomiphene citrate.

Table 9: Comparison in Conception rate

Treatment Regime	*Ovulatory Cycle*	*Conception per ovulatory cycle*	
		Number of conception	*percentage*
CC x 5 days	20	4	20
CC x 10 days	10	3	30

As shown in Table 12 those were treated with 10 days course of 100 mg clomiphene - citrate. Out of 10 cycles - conception occur in 3 ovulatory cycles i. e. in 30% of ovulatory cycle.

Table 10: Cost of Cycle

Treatment regimen	*Tablets*	*Cost of per cycle*
CC (10 days)	20 Tablets	12x10 = 120/-
CC x 5 days	10 Tablets	12x5 = 60/-

Cost of per tablet of 50 mg of clomiphene citrate was Rs 6, so per day cost in 100 mg CC from 10 days cycle was Rs 120. In clomiphene x 5 days treated group cost per cycle was only 60/.

Discussion

DISCUSSION

According to WHO, failure to conceive after 1 year of unprotected intercourse is labelled as infertility. Incidence of infertility in general population is 10-15% (Harrison, 1984; Pepperel, 1984).

Templeton et al. (1990) reported an overall prevalence of infertility as 14%, although half of them eventually conceived. Hull et al. (1985) described the overall prevalence of infertility in U.K. as 17%. In female infertility work up, ovulation is the one of the most important parameter. Ovulatory factor infertility is the most treatable type of infertility.

In the present study, the new regime for ovulation induction was given to patients i. e. 10 days course of clomiphene citrate in 100 mg/day from 2nd day of cycle, those had shown resistant to 5 day course of clomiphene citrate in increasing doses upto 150 mg/day.

Control group had received the 5 day course of clomiphene citrate with human menopausal gonadotropins. Comparison was done for rate of ovulation and cost effectiveness of treatment regimen.

GENERAL CONSIDERATIONS

Infertility may be due to female partner or male partner, in some cases both may be at fault, while in some cases no cause may be found. Figure 1 shows that in the present study, females alone were responsible for 55% of cases and males alone were at fault in 10% cases of infertility. In 25% of cases both partners were accused, In 10% of cases no cause was found

(Table 11).

Factor	*FIGO Manual (1990)*	*Our Study*
Female	25-37%	55%
Male	8-22%	10%
Both	21-38%	25%
Unknown	3-14%	10%

According to FIGQ Manual (1990) female are at fault in a 25-37% of cases and males are responsible for 8-22%,. In 21-38% of cases both partners are responsible while in 3-14% of cases no cause is detected (Table 11).

As contributions of various causes of subfertility varies from country to country and clinic to clinic. A detailed study of the causes of subfertility was seen under WHO between December, 1980 and Sept., 1993 in University Clinic at Kandang Kerbau Hospital. According to that study female infertility is 52.8% which is in accordance to our results i. e. 55%.

According to Emil Novak and coworkers male factors are prevalent in 25-40% of infertility cases. Female factors alone are responsible in 40-55% of cases, both in 10% of cases and 10% of cases are labelled as unexplained infertility,

The incidence of primary and secondary infertility in the present series was reported as 77.50% and 22.50% respectively (Table 2, Figure 2).

lt is in agreement with the result of Panda et al. (1977) from Orissa, who reported the incidence of primary and secondary infertility as 80.04% and 19.06% respectively. Rin et al. (1975) from Tokyo also

reported corresponding results with the incidence as 78.5% and 21.0% respectively.

Saba (1961) and Thomas Adrian et al. (1980) reported a lower incidence of primary infertility. The former reported in Bihar an incidence of 69.5% and 30.5% and the latter workers from Australia reported the incidence of 61.5% and 34.5% of primary and secondary infertility respectively.

Table - 12

Author	*Primary Infertility*	*Secondary Infertility*
Saha (1961)	69.5%	30.5%
Rin et at. (1975)	78.5%	21.5%
Panda et al. (1977)	80.04%	19.06%
Thomas Adrian (1980)	69.5%	30.5%
Present study (1997-98)	77.50%	22.50%

Most of the female partners in the present study were between 21-30 years of age (Table 3). This is in accordance with the results of Panda et al. (1972).

Figure 3 shows that in the present study in the age group of 21-25 years 48.4% of cases belonged to primary infertility group while only 5.44% were grouped under secondary infertility.

Secondary infertility is maximum recorded in 26-30 years of age group i.e. 61.1 %. As the age increased more than 30 years, incidence of infertility was decreased rather we should say less number of patients consulted. But trends are changing, prevalence of infertility in higher age group is increasing (Table 3).

As shown in Figure 4, most of the patients of primary infertility (46.4%, n=30) came for check up and treatment with, in a duration of 5 years or less, after marriage while in the secondary infertility group more patients come after 6-10 years duration of marriage (Table 4). Saba (1961) observed the majority of the patients whether of primary or secondary infertility to have a duration of 6- 10 years of infertility.

According to Figure 5, in our study the contributions of various factors to infertility was, as ovarian factor contributed for more than 50% of cases (n=35), tubal etiology was present in 15.39% (n=10) of cases, uterine and cervical factors were responsible for 9.23% (n=6) and 1.54% (n=l) of cases respectively (Table 5).

Tubal factors were more important in secondary infertility and was responsible for 30% of cases. Uterine factors were cursed in less than 10% cases. Cervical factor may be blammed in less than 2% of cases. In many cases more than one etiology was detected.

Acording to FIGO Manual (1990) ovarian factors are responsible for 26-44% of cases. Tubal factor infertility is present 36-44%. But incidence of tubal factor is very high in Africa i. e. 85% Endometriosis is responsible for 10% of cases (Table 13).

Table 13

Cause	*FIGO Manual (1990)*	*WHO*	*Present study*
Ovulatory factors	26-44 %	23.8%	60.0%
Tubal factors	36-44%	10.6%	22.2%
Endocrinal factor	1-10%	15.8%	11.23%

According to WHO study, ovulatory disorders are present in 23.8% of cases. Tubal causes are present in 10.6%, endometrial and peritoneal factors are responsible for 15.8% of cases and other include 2.5%.

Table 14

Authors	*Average size of follicle*
Hackeloca et al. (Spontaneous)	16-33 mm
Kerin et al. (Spontaneous)	23.62::0.4 mm
Veemesh et al. (Spontaneous)	20.8+0.6 mm
Veemesh et al. (Induced)	25.4:!:1.3 mm
Present study (5 day CC)	19.80 mm
Present study (10 days CC)	21.2 mm

As shown in Table 14, Hachcloeca et al. noted a linear increase in the size of the dominant follicle through a normal menstrual cycle. Developing follicles destined to ovulate increase in size 1-2 mm/day and reach a maximum diameter of 16-33 nun before ovulation.

Kerin et al. reported a mean peak diameter before ovulation was 23.6:!:OA mm. Veermish et al. (1997) compounded the follicular size in spontaneous unstimulated menstrual cycle size of follicle in stimulated cycle was significantly higher than spontaneous cycle.

In the current study average size of follicle with 10 days extended course of clomiphene citrate was 17.04 nun on the 13th day of cycle. This value is in accordance to the size reported by Hackelour et al.

In the normal menstrual cycles, few follicles (less than 10 mm in diameter) that can be imaged throughout the menstrual cycle even during menstruation and pre antral fallicle are too small to be imaged under the influence of follicle stimulation hannone (FSH) released by anterior pituitary gland in response to pulsatile GnRH during the early part of menstrual cycle, a few follicles will undergo progressive development as follicular stimulation progresses. one or occasionally two follicles will continue to develop into the dominant follicles. Many of the developing follicles -will not pass the developmental stage of 10-14 mm diameter before they degenerate.

During the follicular developmental phase one or more follicles may develop. In 5-11% of natural cycles, two dominant follicles may develop, but they are. generally in opposite ovaries.

Table 15

Drugs	***Ovulation rate***
Clomiphene citrate (Standard dose)	<80%
Gonadotrophins	30-100%

Table 20 shows the result of different authors used clomiphen for extended period. Labo et al. used 100 mg CC for 8 days and ovulation was seen in 62% of cycles. R. Fluker et al. used 100 mg clomiphene citrate for 10 days and ovulation was reported in 47% of cycles. In the current study clomiphene citrate was used for 10 days in 100 mg doses per day and ovulation was reported in 66.66% of ovulatory cycles.

Table 16

Authors	Regime	Observations
Lobo et al.	100 mg CC for 8 days	62%
R. Fluker et al.	100 mg CC for 10 days	47%
Present Study	100 mg CC for 10 days	66.66%

In current study ovulation rate with clomiphene citrate 10 days therapy was 66.6%.

As shown in Figure 7 ovulation with 10 days course of clomiphene citrate was 66.66% (n=10) and with clomiphene citrate x 10 days (n= 18).

Table 17 shows the conception rates in two groups.

Author	*CC Regimen*	*Conception Rate*
Lobo et al.	100 mg for 8 days	23%
Fluker el al.	100 mg for 10 day	17%
Current Study	100 mg for 10 day	30%

In current study 10 days course of clomiphene citrate conception rate was 30%, Labo et al. reported conception rate with 8 day course as 23% and Fluker et af. reported conception with 10 days course as 17%.

There is not significant difference in cost of two regimes. So for the poor infertile couples 10 day course of colmiphene citrate is effective method for the ovulation induction, rather than no treatment due to lack of source.

Summary and Conclusion

CONCLUSIONS

The present study was carried out on 80 infertile couples, those attended "Clinic" in MLB Medical College, Jhansi between Ist Sept, 2003 to 30th Aug, 2004.

Cases were evaluated for ovulatory defect. Patients were treated with 10 day course of Clomiphene in 100 mg doses started from 2nd day of period, those had shown resistance to standard 5 day course of clomiphene upto 150 mg/day doses started from 2nd day of period. Comparison was done with patients receiving clomiphene citrate. 15 cases were treated with 10 days course of clomiphene citrate and compared with 35 patients treated with clomiphene x 5 days. The following conclusions have been drawn:

1. For the infertility male and female both were responsible. Females alone were responsible for 550/0 of cases. Male alone were responsible for 10% of cases. Male and female both were responsible for 25% of cases while 10% of cases, labelled as unexplained infertility.

2. The incidence of primary infertility was 77.50% and that of secondary infection was 22.500/0.

3. The incidence of infertility was maximum in 21-30 years of age. Primary infertility was more in 21-25 years of patients i.e. 46.4% while secondary infertility was more in 26-30 years aged patients and that were 61.10/0.

4. Primary infertility was more prevalent in first 5 years of marriage that was' 46.780/0. Secondary infertility was more prevalent in the 6-10 years of marriage that was 44.44%.

5. The most important cause of infertility was ovulatory defect in both type of infertility. In primary infertility, ovulatory factors alone were responsible for 55.550/0 of cases, while in secondary infertility group 35% of cases were noted. Tubal factors are more important in secondary infertility than primary infertility i.e. 30% and 8.890/0 respectively.

Incidence of uterine factors was less than 100/0 in both groups. Cervical factors were responsible for 2.220/0 of cases of primary infertility. In 6.67% of cases of primary infertility tubal and ovarian both factors were present. In another 6.67% of cases ovarian and uterine both factors were present. In 8.89% of primary infertility tubal and uterine factors were present. There was one case (2.22%) in which tubal, ovarian and uterine three factors causing infertility were present. The same patient also had infertility, contributed with her husband.

In secondary infertility group 6.150/0 cases were allotted to each group i. e. tubal and ovarial, tubal and uterine factor and ovarian and uterine factor defects.

6. Average size of follicle just before the ovulation with 5 days course of clomiphene citrate was 19.8 mm while with x 10 days was 21.2 min.

7. Average day of ovulation in patients treated with 5 days course of clomiphene citrate was 14 and in patients CC 10 days treated with was 15.

8. Ovulation rate with 10 day course of clomiphene citrate was 66.66% and that with x 5 days 57%.

9. Conception occurred in 30% of ovulatory cycle in patients treated with 10 day course of clomiphene citrate and 20% of ovulatory cycles in CC 5 days.

10. There was not significant difference in cost of two cycles. Cost per cycle of CC for 10 days was Rs 120/- while cost per cycle of x 5 days was Rs 60/-.

11. No evidence of ovarian hyperstimulation in any induced cycle was seen.

12. In none of the induced cycle any other side effect of CC as visual disturbances, vasomotor flushes, nausea, pelvic discomfort or breast pain was reported.

In the end it is concluded that 10 day course of clomiphene citrate is simple, safe, non-invasive and cost effective form of treatment for poor infertile couples, those may not afford the gonadotrophins.

SUMMARY

Infertility is the inablity to conceive after 1 year of unprotected intercourse (WHO). Ovulation is one of the most important prerequisite for the . fertility. Ovulatory disorders are responsible for 26-40% of all cases of female infertility. It is the most easily diagnosed and most treatable cause of infertility.

There is a Plethora of drugs "to overcome ovulatory defect and to induce ovulation. These drugs are clomiphene citrate, other anti estrogenic drugs, human menopausal gonadotrophins and gonadotrophins releasing hormones.

These drugs may be given alone or in combination, in different doses with different route, in different regimes according to type of ovulatory defect.

In the present study 80 infertile couples were studied. Out of 80 couples 35 females were having ovulatorydefect. They were grouped in cases and control groups. 15 patients were labelled as cases, they received 100 mg of clomiphene citrate for 10 day from 2nd day of cycle after showing resistance to 150 mg/day clomiphene citrate for 5 days. 20 patients were labelled as controls and they received 100 mg of clomiphene per day from 2nd day of cycle for 5 days with Human menopausal gonadotrophins according to follicular growth and ovulatory response.

Transvaginal ultra sonography was used for the monitoring of follicular development and detection of ovulation.

Following inferences were drawn from the study:

1. For the infertility male and female both were responsible. Females alone were responsible for 55% of cases. Male alone were responsible for 10%of cases. Male and female both were responsible for 25% of cases while 10% of cases, labelled as unexplained infertility.

2. The incidence of primary infertility was 77.50% and that of secondary infertility was 22.50%.

3. The incidence of infertility was maximwn in 21-30 years of age. Primary infertility was more in 21-25 years of patients i.e. 46.4% while secondary infertility was more in 26-30 years aged patients and that were 61.1%.

4. Primary infertility was more prevalent in first 5 years of marriage that was 46.780/0. Secondary infertility was more prevalent in the 6-10 years of marriage that was 44.44%.

5. The most important cause of infertility was ovulatory defect in both type of infertility. In primary infertility, ovulatory factors alone were responsible for 55.550/0 of cases, while in secondary infertility group 35% of cases were noted. Tubal factors are more important in secondary infertility than primary infertility i. e. 30% and 8.89% respectively.

   Incidence of uterine factors was less than 10% in both groups. Cervical factors were responsible for 2.22% of cases of primary infertility. In 6.67% of cases of primary infertility tubal and ovarian both factors were present. In another 6.67%.of cases ovarian'and

uterine both factors were present. In 8.89% of primary infertiJity tubal and uterine factors were present. There was one case (2.220/0) in which tubal, ovarian and uterine three factors causing infertility were present. The same patient also had infertility, contributed with her husband In secondary infertility group 6.15% cases were allotted to each group i. e. tubal and ovarial, tubal and uterine factor and ovarian and uterine factor defects'

6. Average size of follicle just before the ovulation with 5 days course of clomiphene citrate was 19.8 mm while with clomiphene with 10 days it was 21.2 mm.

7. Average day of ovulation in patients treated with 10 days course of clomiphene citrate was 15 and in patients treated with CC 5 days was 14.

8. Ovulation rate with 10 days course of clomiphene citrate was 66.66% and that with clomiphene for 5 days was 57%.

9. Conception rate CC 10 days course was 30% & with 5 days course was 20%.

10. There was not significant difference in cost of two cycles. Cost per cycle of CC for 10 days was Rs. 120/- while cost per cycle for 5 days was 60/-.

11. No evidence of ovarian hyperstimulation in any induced cycle was seen.

12. In none of the induced cycle any other side effect of CC as visual disturbances, vasomotor flushes, nausea, pelvic discomfort or breast pain was reported.

In the end It is concluded that 10 day course of clomiphene citrate is simple,safe, non-invasive and cost effective form of treatment for poor infertile couples, those may not afford the gonadotrophins.

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